

## Effects of Reduced Kidney Function Because of Living Kidney Donation on Left Ventricular Mass

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**Abstract**—Living kidney donation is associated with a small but significant increase in cardiovascular mortality. In addition, mildly decreased kidney function is associated with an increase of left ventricular mass and with cardiovascular disease in patients with chronic kidney disease. To investigate this association, we evaluated the impact of mildly decreased kidney function after living kidney donation on subclinical cardiac structural and functional changes. In this prospective cohort study, cardiac and renal magnetic resonance imaging and laboratory analyses were performed in 23 living kidney donors (mean age 54±10 years, 52% male) before donation and at 4 and 12 months after nephrectomy. Mean estimated glomerular filtration rate was 102±15 mL min<sup>-1</sup> 1.73 m<sup>-2</sup> before donation and 70±13 mL min<sup>-1</sup> 1.73 m<sup>-2</sup> at 12 months ( $P<0.001$ ). Left ventricular mass increased from 112±22 to 115±23 g ( $P<0.001$ ). In addition, heart rate was significantly increased (65±7 to 74±14;  $P=0.04$ ). Concurrently, kidney and adrenal gland volume increased from 163±33 to 195±34 mL ( $P<0.001$ ) and from 7.6±2.2 to 8.4±2.4 mL ( $P=0.032$ ), respectively, as did procollagen type III ( $\Delta 0.11$  ng/mL,  $P<0.001$ ) and not N-terminal probrain natriuretic peptide ( $\Delta 14$  pg/mL,  $P=0.25$ ). The mild decrease in kidney function after living kidney donation leads to a significant but clinically negligible increase in left ventricular mass 12 months after living kidney donation. This study of a longitudinal analysis of living kidney donors provides direct evidence of a kidney–heart link. (*Hypertension*. 2017;69:297–303. DOI: 10.1161/HYPERTENSIONAHA.116.08175.) • [Online Data Supplement](#)

**Key Words:** glomerular filtration rate ■ heart rate ■ hypertrophy ■ left ventricular remodeling ■ magnetic resonance imaging ■ nephrectomy ■ transplantation, renal

Left ventricular hypertrophy is an important cardiovascular risk factor<sup>1,2</sup> and is common in chronic kidney disease.<sup>3,4</sup> Increased left ventricular mass (LVM) is an early subclinical predictor of cardiovascular disease and associated with mild kidney function impairment independent of traditional risk factors, suggesting a pathophysiological link between kidney function and cardiac patterns.<sup>5,6</sup> Recent animal experiments demonstrated structural and functional changes and altered gene expression in the left ventricular myocardium after unilateral nephrectomy.<sup>7,8</sup>

Importantly, recent observational data have shown a small but significant increase in cardiovascular mortality in living kidney donors compared with matched healthy controls.<sup>9</sup> This risk may be explained by adverse effects of mildly reduced kidney function on cardiac and vascular function. Living kidney donation (LKD) allows studying the effects of mildly impaired renal function on LVM without major confounding<sup>10</sup> which may be found in patients experiencing mild renal disease as well.

Thus, we designed a study to assess temporal changes of cardiac and renal parameters after LKD. We hypothesized that a loss in kidney function in living kidney donors is associated with an increase in LVM and in residual kidney volume in line with renocardiac functional and structural adaptation processes. To address this aim, we prospectively assessed LVM, cardiac remodeling, and function, as well as kidney and adrenal mass and function in living kidney donors by magnetic resonance imaging (MRI) and laboratory parameters before and ≤12 months after nephrectomy.

### Methods

#### Study Design

This prospective observational study was performed at the Universitätsklinikum Regensburg. The study protocol was reviewed and approved by the local ethic committee, adhered to the principles set out by the Declaration of Helsinki. Written informed consent was obtained from all participants at enrollment into the study.

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Potential living kidney donors were identified in the living donor kidney transplant program at the Interdisciplinary Transplantation Center at the Universitätsklinikum Regensburg from September 2009 to February 2012. LKD was approved by the local independent living donation committee before the donor nephrectomy. In addition to conventional donor selection criteria, contraindications for MRI led to an exclusion from this study. The subjects were invited to magnetic resonance scans and laboratory analysis at 3 predefined time points: 1 day before kidney donation (baseline examination) and at 4 and 12 months after surgery for follow-up data. In a subsample of 8 participants, an additional MRI examination was performed 4 months before donation to exclude a potential increase in LVM independent of LKD. Transplantation surgery was performed at the Universitätsklinikum Regensburg applying the mini-incision technique.<sup>11</sup>

Primary end point of the study was the change in LVM between baseline and 12 months after LKD, determined by MRI. Secondary end points were changes in systolic and diastolic cardiac function, cardiac wall thickness, kidney and adrenal gland volume, estimated glomerular filtration rate (GFR), aldosterone:renin ratio, proteinuria, N-terminal probrain natriuretic peptide, and procollagen type III between baseline, 4, and 12 months after LKD.

### Laboratory Analysis

Blood samples were collected to measure the following parameters: serum creatinine for estimating clearance (Cockcroft–Gault) and estimated GFR (Chronic Kidney Disease Epidemiology Collaboration [2009] creatinine equation)<sup>12</sup>; aldosterone and renin after 30 minutes of rest and the aldosterone:renin ratio for the assessment of the renin–angiotensin–aldosterone system<sup>13,14</sup>; procollagen type III as an indicator for cardiac fibrosis<sup>15</sup> and N-terminal probrain natriuretic peptide. Urinary protein concentration in midstream urine samples was divided by urinary creatinine concentration to estimate daily excretion of protein.

### Physical Examination

At each visit, measurements of heart rate, systolic and diastolic blood pressure, and of body weight and height were taken. Study participants sat in an isolated room, and heart rate and blood pressure were measured thrice using an oscillometric sphygmomanometer (DINAMAP 1846SX; Critikon Inc) with a cuff size appropriate for arm diameter after for 30 minutes of rest. The mean of the last 2 measurements was used in analysis.<sup>16,17</sup> After measurement of blood pressure and heart rate, blood samples for measurement of renin and aldosterone were obtained. In addition, donors were asked whether their activity status had returned to the predonation level at the 4- and 12-month follow-up visits.

### Cardiac MRI

Cardiac magnetic resonance images were acquired using a clinical 1.5-Tesla scanner (MAGNETOM Avanto; Siemens Healthcare Medical Solutions, Erlangen, Germany) with standard spine and body phased-array coils, retrospectively ECG triggered. Subjects were examined in a supine position within the scanner. Cine short-axis and long-axis slices were obtained with a steady-state-free precision gradient-echo sequence (SSFP-sequence; trueFISP). Standardized imaging parameters included: repetition time 60.06 ms, echo time 1.16 ms, flip angle 74°, and a voxel size of 2.2×1.6 mm. Left ventricle was continuously recorded from base to apex in short-axis slices with a slice thickness of 8.0 mm. To encompass the entire left ventricle, an average of 8 short-axis segments with 25 frames per cardiac cycle was needed. Using analytic contour recognition software (Argus, syngo MR B15; Siemens Healthcare Medical Solutions), endocardial and epicardial borders were carefully manually retraced in each left ventricular short-axis image at end diastole and end systole. To normalize the ascertained results to body surface, the Formula by DuBois was used. For primary analysis, left ventricular papillary muscles were excluded from mass measurements. Because of controversial statements in literature for the general inclusion of papillary muscle mass, complete procedure was performed once more, this time including papillary muscles to total myocardial mass.<sup>18</sup> Septal and posterior wall thicknesses were measured midventricular

in end-diastolic short-axis segments. The correlation of LVM to left ventricular end-diastolic volume was calculated as an index of concentric remodeling. For diastolic function, peak filling rate and time to peak filling rate were analyzed.

To reduce potential deviations to a minimum, all magnetic resonance scans were performed in accordance to a standardized protocol and were analyzed by a single observer. To assess the intraobserver reproducibility, magnetic resonance scans of 10 randomly selected subjects were reanalyzed at 2 different points in time. Statistical comparison showed no significant variations in LVM (103.9±15.8 versus 104.5±15.8 g;  $P=0.164$ ). The intraclass correlation between both measurements was 0.995.

### Kidney and Adrenal Gland MRI

Axial fat-saturated spoiled-gradient echo sequence was used for volume measurements. The parameters for this sequence were as follows: volumetric interpolated breath-hold examination with 60 slices (TR/TE=4.58 ms/1.66 ms; flip angle=10°; matrix size=192×300; field of view=380×380 mm, slice thickness 2.5 mm). All data were transferred to a workstation with ITK-snap for postprocessing<sup>19</sup> (<http://www.itksnap.org/pmwiki/pmwiki.php>) and was analyzed by a single observer. To calculate the voxel count volume of kidneys and adrenal, images were analyzed slice-by-slice, tracing the boundaries of the kidneys and adrenals at several levels and interpolating the intervening slices using a semiautomated algorithm. Next, renal and adrenal volume was calculated by summing up all voxel volumes lying within those boundaries.

### Statistical Analysis

Depending on the underlying distribution, continuous variables are presented either as mean values and SD or as median values and interquartile ranges ( $P_{25}$ ;  $P_{75}$ ); categorical variables are presented as absolute numbers and proportions. To analyze the change of LVM and further cardiac, clinical, and laboratory data over time, linear mixed models were used. Non-normal distributed variables were analyzed by linear mixed models based on ranks. The correlation structure

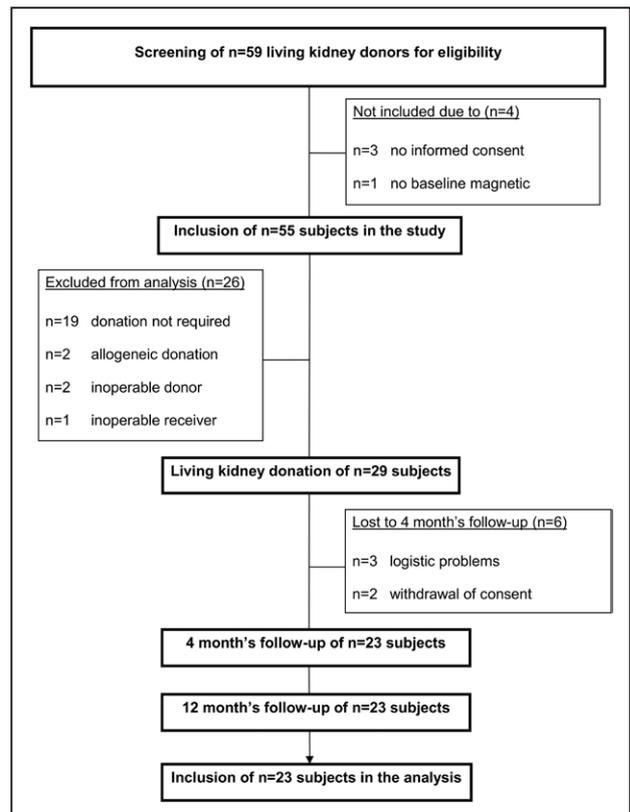


Figure 1. Trial profile of participants during the study.

between the 3 time points, baseline, 4-month, and 12-month follow-up, was specified as unstructured. We provided mean values and SDs or median values and interquartile ranges as parameter estimates and adjusted the pairwise comparisons by the Tukey–Kramer method. Additional models were calculated to analyze differences in LVM change (baseline to 12-month follow-up) on age, sex, smoking status, initial systolic blood pressure, baseline weight, and baseline LVM. Differences in LVM between 4 months before surgery and baseline were analyzed using a paired *t* test. Inter-rater agreement was assessed by use of the intraclass correlation coefficient (2.1, absolute agreement). All reported *P* values are 2-sided, and a *P* value of 0.05 is considered the threshold of statistical significance. Because of the exploratory nature of our trial, no *P* value adjustment was performed for the linear mixed models. Data entry and calculations were made with the software package SPSS 21.0 (IBM, Chicago, IL), and the linear mixed model analyses were undertaken using the SAS 9.3 procedure PROC MIXED (SAS Institute, Cary, NC).

**Results**

**Study Participants**

Between October 2009 and February 2012, a total of 59 consecutive potential living kidney donors were screened for eligibility at the Universitätsklinikum Regensburg, of whom 55 subjects fulfilling the inclusion criteria were enrolled in the study. The trial profile of this prospective study is shown in Figure 1. Among the 55 subjects recruited, 29 subjects underwent surgery during the observation period, of which 23 donors completed follow-up examination at 4 and 12 months after donation and were included in the analysis. All living kidney donors showed normal activity status by the 4-month follow-up visit, except for 1 donor experiencing prolonged wound pain. No living kidney donor had surgical complications, and no donor died in the follow-up period.

**Baseline Characteristics**

Baseline demographic and clinical characteristics of the living kidney donors are summarized in Table 1. There were 11 male and 12 female subjects. The mean age was 54±10 years. At baseline, all subjects had sinus rhythm with a heart rate of 65±7 min<sup>-1</sup>. Mean blood pressure was 128/81 mmHg. Six subjects had known treated arterial hypertension. No subject presented with diabetes mellitus.

**Clinical Parameters**

Heart rate significantly increased within 12 months after donation (65±7 versus 74±14 min<sup>-1</sup>; *P*=0.033). Systolic and diastolic blood pressure remained unchanged at the 4- and 12-month follow-up (Table 2). The body weight (76.4±12.2 versus 76.9±13.4 kg; *P*=0.389) and BMI (25.5±2.5 versus 25.6±2.5 kg/m<sup>2</sup>; *P*=0.520) was stable over 12 months.

**Kidney Function and Biomarker Analysis**

At 12 months after LKD, plasma creatinine concentration increased from 0.84±0.16 to 1.21±0.27 mg/dL (*P*<0.001; Table 2; Table S1 in the [online-only Data Supplement](#)). At the 12-month follow-up, GFR decreased from 102±15 mL min<sup>-1</sup> 1.73 m<sup>-2</sup> before donation to 70±13 mL min<sup>-1</sup> 1.73 m<sup>-2</sup> as measured by Chronic Kidney Disease Epidemiology Collaboration (*P*<0.001). Compared with baseline, proteinuria increased from 85 (57; 156) mg/g creatinine to 155(85; 229) mg/g creatinine (*P*=0.040) at 12 months after donation.

No living kidney donor progressed to end-stage renal disease during follow-up.

The aldosterone:renin ratio was significantly increased at 4- (10.4 [3.8; 13.7]; *P*=0.01) and 12-month follow-up (10.7 [3.7; 14.3]; *P*=0.03) compared with baseline. Procollagen type III significantly increased at 4 months (0.45±0.11 versus 0.58±0.11 ng/mL; *P*<0.001) and persisted at this level (0.56±0.14 ng/mL; *P*<0.001) at 12-month follow-up. Compared with baseline values, N-terminal probrain natriuretic peptide was nonsignificantly elevated at 12 months (64 [35;116] versus 78 pg/mL [48;159]; *P*=0.25).

**Left Ventricular Mass**

Baseline cardiac MRI data are presented in Table 3. At baseline, LVM values ranged from 79 to 159 g with a mean value of 112±22 g. A preexisting left ventricular hypertrophy could be excluded.

Between baseline and the 4-month follow-up, LVM significantly increased by 1.6 g (*P*<0.001), corresponding to a relative increase of 1.5% (95% confidence interval, 1.0–1.9%; *P*<0.001) from baseline LVM. LVM further increased by 1.5 g (*P*<0.001) between the 4- and 12-month follow-up. Twelve months after LKD, total LVM significantly

**Table 1. Baseline Characteristics**

Characteristic	
N	23
Age, y	54±10
Male sex, n (%)	11 (48)
Body mass index, kg/m <sup>2</sup>	25.3±2.3
Body surface area, m <sup>2</sup>	1.89±0.20
Right-sided donation, n (%)	19 (83)
Hypertension, n (%)	6 (28)
Diabetes mellitus, n (%)	0 (0)
Smoker, n (%)	3 (13)
Systolic blood pressure, mm Hg	129±14
Diastolic blood pressure, mm Hg	76±8
Heart rate, min <sup>-1</sup>	65±7
Estimated creatinine clearance (CG), mL/min	101±23
eGFR (CKD-EPI), mL min <sup>-1</sup> 1.73 m <sup>-2</sup>	91±17
Serum creatinine, mg/dL	0.84±0.16
Cystatin C, mg/L	0.69±0.12
Proteinuria, mg/g creatinine	85 (57; 156)
Aldosterone, pg/mL	54 (29; 67)
Plasma renin, pg/mL	9.2 (6.7; 24.8)
Aldosterone:renin ratio	3.6 (2.2; 9.7)
Procollagen type III, ng/mL	0.45±0.11
NT-proBNP, pg/mL	64 (35; 116)

All data are expressed as n (%), mean±SD or median (1st quartile; 3rd quartile). CG indicates Cockcroft–Gault; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; and NT-proBNP, N-terminal probrain natriuretic peptide.

**Table 2. Clinical and Laboratory Data Between Baseline, 4 Months and 12 Months After Living Kidney Donation**

Variable	Baseline	4 mo	12 mo	PValue, Baseline, fu12	PValue, Baseline, fu4	PValue, fu4–fu12
Systolic blood pressure, mm Hg	129±14	128±19	131±18	0.83	0.94	0.64
Diastolic blood pressure, mm Hg	76±8	76±8	77±10	0.18	0.021	0.88
Heart rate, min <sup>-1</sup>	65±7	69±11	74±14	0.04	0.24	0.10
eCC (CG), mL/min	101±23	69±15	71±15	<0.001	<0.001	0.08
eGFR (CKD-EPI), mL min <sup>-1</sup> 1.73 m <sup>-2</sup>	102±15	71±13	70±13	<0.001	<0.001	0.993
Serum creatinine, mg/dL	0.84±0.16	1.24±0.25	1.21±0.27	<0.001	<0.001	0.57
Cystatin C, mg/l	0.69±0.12	0.97±0.23	0.99±0.17	<0.001	<0.001	0.97
Proteinuria, mg/g creatinine	85 (57; 156)	167 (87; 255)	155 (85; 229)	0.040	0.053	0.961
Aldosterone, pg/mL	54 (29;67)	63 (43;75)	52 (35;87)	0.58	0.24	0.37
Plasma renin, pg/mL	9.2 (6.7;24.8)	5.7 (3.8;14.4)	7.9 (4.2;15.4)	0.11	0.04	0.72
Aldosterone:renin ratio	3.6 (2.2;9.7)	10.4 (3.8;13.7)	10.7 (3.7;14.3)	0.03	0.01	0.77
Procollagen type III, ng/mL	0.45±0.11	0.58±0.11	0.56±0.14	<0.001	<0.001	0.24
NT-proBNP, pg/mL	64 (35;116)	71 (30;181)	78 (48;159)	0.25	0.19	0.81

All data are expressed as n (%), mean±SD or median (1st quartile; 3rd quartile). CG indicates Cockcroft–Gault; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eCC, estimated creatinine clearance; eGFR, estimated glomerular filtration rate; fu, follow-up; and NT-proBNP, N-terminal probrain natriuretic peptide

increased to 115±23 g ( $P<0.001$ ), corresponding to a relative increase of 2.8% compared with baseline LVM (95% confidence interval, 2.2–3.3%;  $P<0.001$ ) (Table 3, Table S2; Figure 2A).

Similar results were obtained when papillary muscle mass was added to total LVM or when LVM was indexed to body surface area (Table 3). The observed increase in left ventricular septal wall thickness (9.6±1.6 versus 10.0±2.0 mm;  $P=0.17$ ) and posterior wall thickness (8.1±1.3 versus 8.8±1.7 mm;  $P=0.10$ ) was not statistically significant. Cardiac remodeling as described by the LVM/end-diastolic

volume ratio significantly increased from baseline compared with the 12-month follow-up (0.97±0.1 versus 1.06±0.2;  $P<0.001$ ).

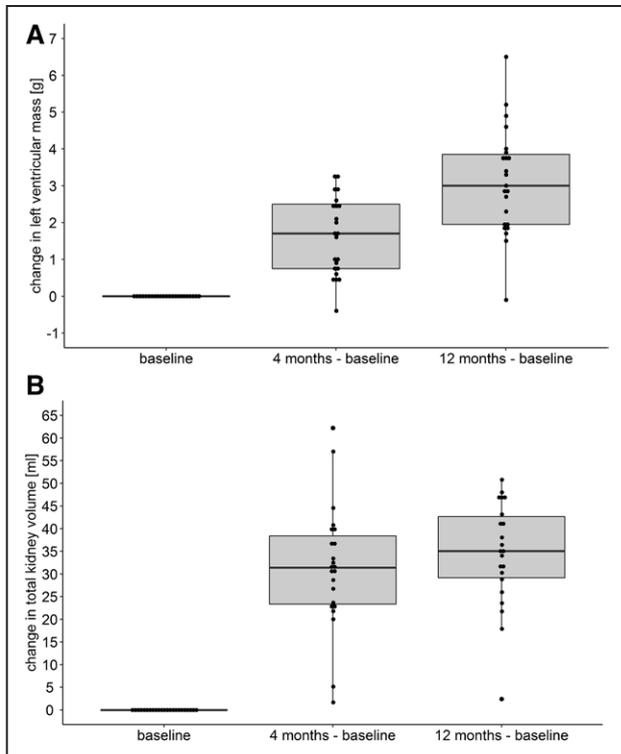
By analyzing the dependency of LVM change on the variables age, sex, baseline systolic blood pressure, baseline weight, baseline GFR, and baseline heart rate, none of these variables showed a significant relationship to  $\Delta$ LVM.

The study is based on the assumption that without a basic event LVM does not change significantly within a period of several months. This was verified by a subgroup analysis (intracontrol group) that showed no significant change in

**Table 3. Cardiac Magnetic Resonance Parameters Between Baseline, 4 Months, and 12 Months After Living Kidney Donation**

Variable	Baseline	4 mo	12 mo	PValue, Baseline, fu12	PValue, Baseline, fu4	PValue, fu4–fu12
LVM, g	112±22	114±23	115±23	<0.001	<0.001	<0.001
LVM index, g/m <sup>2</sup>	59±7	60±8	60±7	<0.001	0.006	0.635
LVM+Pap, g	118±24	120±24	122±25	<0.001	<0.001	<0.001
LVM+Pap index, g/m <sup>2</sup>	62±8	63±9	64±8	<0.001	0.002	0.113
LVM/EDV, g/mL	0.89±0.12	0.90±0.12	0.95±0.16	0.015	0.84	0.019
SWT, mm	9.6±1.6	9.8±1.6	10.0±2.0	0.17	0.70	0.24
PWT, mm	8.1±1.3	8.1±1.8	8.8±1.7	0.10	0.99	0.18
EF, %	65±6	65±5	66±5	0.90	0.89	0.58
EDV, ml	126±19	127±19	122±18	0.18	0.98	0.08
ESV, ml	44±12	45±12	42±11	0.38	0.94	0.18
Peak filling rate, mL/s	326±73	302±70	284±57	0.003	0.12	0.19
Time to peak filling rate, ms	141±18	149±20	148±20	0.09	0.19	0.84

All data are expressed as n (%), mean±SD. EDV indicates end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; fu, follow-up; LVM, left ventricular mass; Pap, papillary muscle mass; PWT, posterior wall thickness; and SWT, septal wall thickness.



**Figure 2.** **A**, Change in left ventricular mass between baseline, 4 mo, and 12 mo after living kidney donation. **B**, Change in renal volume between baseline, 4 mo, and 12 mo after living kidney donation.

LVM within 4 months before nephrectomy ( $117.0 \pm 25.0$  versus  $116.8 \pm 25.3$  g;  $P=0.16$ ; Table S3).

**Systolic and Diastolic Cardiac Function**

At 4 and 12 months after LKD, left ventricular systolic function was preserved with no significant changes in ejection fraction, end-diastolic or end-systolic volumes (Table 3). Diastolic peak filling rate decreased significantly from baseline to 12-month follow-up ( $326 \pm 73$  versus  $284 \pm 57$  mL/s;  $P=0.003$ ). Diastolic time to peak filling rate did not change significantly ( $141 \pm 18$  versus  $148 \pm 20$  ms;  $P=0.09$ ).

**Kidney and Adrenal Gland Volume**

At baseline, the volumes of the remaining kidney ranged from 112 to 229 mL with a mean of  $163 \pm 33$  mL. At 4 months after LKD, the kidney volume significantly increased to  $194 \pm 32$  mL ( $P<0.001$ ) and remained unchanged at 12 months ( $195 \pm 34$  mL;  $P=0.53$ ; Figure 2B), confirming results of previous studies on compensatory hypertrophy of the remnant kidney after contralateral nephrectomy. Total adrenal gland volume increased from  $7.6 \pm 2.2$  to  $8.4 \pm 2.4$  mL ( $P=0.032$ ; Table S2).

**Discussion**

In this prospective study examining the effects of LKD on structure and function of the kidney and heart, we observed the following key findings at 4 and 12 months after unilateral nephrectomy:

First, there is a small but significant increase in LVM after LKD that is independent of traditional risk factors of LVM increase. Second, diastolic function is mildly impaired after

LKD. Third, procollagen type III as a biomarker of cardiac fibrosis is increased. Fourth, the kidney volume increased significantly. Finally, adrenal gland volume increased with a concurrent increase in aldosterone:renin ratio.

It is well known that mildly reduced kidney function is associated with increased LVM,<sup>20,21</sup> which is an early subclinical predictor for cardiovascular disease.<sup>22,23</sup> Several mechanisms may explain the association of reduced GFR with increased LVM observed in our study.

Arterial hypertension is an important cause of left ventricular hypertrophy, and blood pressure values tend to increase after LKD.<sup>24,25</sup> However, blood pressure was essentially unchanged in the 12-month follow-up period after LKD in our study, thus excluding hypertension as the cause of LVM in our donors.

Natriuretic peptides can be directly triggered by acute reduction of renal mass, as evidenced in animal studies.<sup>26</sup> N-terminal probrain natriuretic peptide was increased slightly at 12 months in our study. This is in line with a previous study of LKD in which natriuretic peptide concentrations of donors were higher compared with those of healthy volunteers.<sup>10</sup> Similar to our results, the natriuretic peptides levels were still within normal range.

Further, an activated renin–aldosterone system is observed after acute reduction of renal mass<sup>27</sup> and plays a key role in the pathogenesis of cardiac fibrosis.<sup>28–30</sup> Indeed, our study shows adrenal gland hypertrophy and an increase of the aldosterone:renin ratio,<sup>13,14</sup> suggesting that sympathetic activation may be involved in the postnephrectomy hypertrophy of the heart and remnant kidney. Although an activation of the renin–aldosterone system has been shown in patients with chronic kidney disease,<sup>8,31</sup> adrenal hypertrophy has been described only in animal studies.<sup>29,32</sup>

Further, aging is an unlikely mechanism of development of LVM because echocardiographic studies in the healthy general population have shown that there is no increase of LVM with age after adjusting for body surface area.<sup>33–35</sup>

Finally, other potential mechanisms induced by kidney growth itself,<sup>36–38</sup> as demonstrated by the increase in kidney volume, may be involved in inducing structural and functional changes in the heart. This includes activation of systemic inflammatory transforming growth factor- $\beta$  and apoptotic pathways<sup>7,38,39</sup> as observed in rats developing an early increase of myocardial collagen content, LVM increase, and alterations in diastolic function after unilateral nephrectomy. Our study was not designed to detect cardiac fibrosis. However, procollagen type III a biomarker for cardiac fibrosis<sup>40,41</sup> significantly increased after nephrectomy and remained elevated at 12 months, suggesting a possible role of cardiac fibrosis in increasing LVM after LKD.

**Implications**

Our findings have several important implications. Recent data from the Norwegian LKD registry have shown an increase in overall and cardiovascular mortality many years after LKD,<sup>9</sup> and left ventricular hypertrophy is associated with cardiovascular end points.<sup>18,19</sup> However, we do not think that the small (but significant) increase in LVM or early diastolic left ventricular dysfunction we observed after LKD is clinically relevant or will even progress to left ventricular hypertrophy or jeopardize the patient’s life. Indeed, the increase in relative risk for cardiovascular mortality observed after LKD is only 40% in the study by

Mjøen et al,<sup>9</sup> whereas other factors such as male sex and smoking double the risk of cardiovascular mortality after LKD. In addition, the increase in heart rate after LKD implies an important role of the sympathetic system in inducing LVM increase after LKD. Further work is indeed to determine whether this is generalizable to patients with chronic kidney disease.

### Strengths and Limitations

Strengths of our study include the prospective design, the use of MRI as the gold standard in cardiac imaging and the detailed analysis of imaging and biomarker data. Further, previous studies examining the relationship of kidney function with LVM were typically performed in cohorts not excluding diseases leading to kidney function impairment, for example, hypertension and diabetes mellitus, suggesting that these associations may have been confounded. The limitation of these studies does not apply to our longitudinal analysis of living kidney donors, where unilateral nephrectomy leads to sudden isolated reduction in kidney function at a known time point without changing the individual's health status.

However, some limitations warrant consideration. First, our results in healthy living kidney donors may not be generalizable to patients with chronic kidney disease with similar kidney function impairment because concomitant diseases such as arterial hypertension in chronic kidney disease patients may aggravate progression of LVM. Second, we did not perform analyses in healthy individuals who did not donate a kidney. However, an intracontrol group of study participants prospectively analyzed for change of LVM before nephrectomy and showed no significant changes in LVM. Third, we did not perform direct measurements of sympathetic activation (eg, 24-hour urine collection of catecholamine) to confirm the hypothesis of a link between adrenal hypertrophy and LVM increase via the sympathetic system. However, the observed increase in heart rate indirectly supports this hypothesis. Fourth, 24-hour ambulatory blood pressure was not performed for logistic reasons and could influence the results and potentially limiting the representativity of the blood pressure determinations at each visit. However, blood pressure measurements were performed in an isolated room with a long time of rest. Others have shown that this improves reproducibility and provides office blood pressure values closer to those obtained by daytime ambulatory blood pressure measurements.<sup>16,17</sup> Finally, we did not have data from independent cohort to confirm our results of this single-center study with limited sample size.

### Perspectives

Mild kidney function impairment induced by unilateral human nephrectomy is independently associated with significant but clinically irrelevant cardiac changes. This effect is associated with increased adrenal gland volume and may therefore also be mediated by sympathetic activation. In addition, there is evidence for an involvement of the renin-angiotensin-aldosterone system. The current results provide direct evidence for the link between kidney and heart in humans.

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### Disclosures

None.

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## Novelty and Significance

### What Is New?

- Increased left ventricular mass is an early subclinical predictor of cardiovascular disease and seems to be associated to mild renal disease. Because it is rather difficult to detect patients with early-stage renal disease without comorbidities, living kidney donors offer an inimitable model for this question. Furthermore, living kidney donation seems to be associated with increased cardiovascular risk. We have shown that mild reduction in renal function caused by living kidney donation is independently associated with increased left ventricular mass, increased renal, and adrenal gland mass.

### What Is Relevant?

- Mildly reduced renal function seems to be associated with increased left ventricular mass which is an early subclinical predictor for cardiovas-

cular disease. Consequently, a kidney–heart connection seems to exist leading to remodeling processes in the heart and the kidney. This is based on clinical and epidemiological observations that both kidney failure and cardiac structural changes are associated with a high incidence of failure of the other organ.

### Summary

This study, a model of mild renal disease with living kidney donors, shows that mild kidney function impairment induced by nephrectomy is independently associated with significant structural and functional changes of the heart, kidney, and adrenal gland with evidence for an involvement of the renin–angiotensin–aldosterone system.

## Effects of Reduced Kidney Function Because of Living Kidney Donation on Left Ventricular Mass

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## ***Supplementary appendix***

# **Effects of reduced kidney function due to living kidney donation on left ventricular mass**

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**Short title:** Subclinical left ventricular hypertrophy caused by unilateral nephrectomy

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## Supplementary appendix

**Table S1. Changes in clinical and laboratory data between baseline, four months and 12 months after living kidney donation**

Variable	n	fu4 - baseline	n	fu12 - fu4	n	fu12 - baseline
Systolic blood pressure, mmHg	23	-1±18	23	3±15	23	2±14
Diastolic blood pressure, mmHg	23	-1±10	23	1±10	23	0±11
Heart rate, min <sup>-1</sup>	23	4±10	23	5±11	23	9±16
eCC (CG), ml/min	22	-32±12	22	2±6	23	-30±13
eGFR (CKD-EPI), ml/min	23	-33.1±8.6	23	-0.17±8.4	23	-31.8±7.1
Serum creatinine, mg/dl	23	0.40±0.13	23	-0.03±0.13	23	0.37±0.16
Cystatin C, mg/l	22	0.30±0.19	21	0.01±0.17	18	0.29±0.09
Proteinuria mg/g creatinine	23	62.4 (-15.7, 148.3)	23	-25.5 (-74.6, 63.1)	23	53.2 (-12.3, 100.5)
Aldosterone, pg/ml	16	7.5 (-16.0;37.5)	20	-1.0 (-28.5;16.5)	16	2.5 (-9.0;22.0)
Plasma renin, pg/ml	17	-1.5 (-3.7;-0.5)	20	-0.9 (-3.1;2.1)	17	-2.5 (-8.8;2.3)
Aldosterone-to-renin ratio	16	3.1 (-0.2;8.1)	20	0.2 (-2.5;3.2)	16	0.8 (-3.5;5.1)
Procollagen-type-III, ng/ml	20	0.12±0.10	20	-0.03±0.13	20	0.09±0.12
NT-proBNP, pg/ml	21	4 (-14;24)	22	10 (-30;34)	22	25 (-3;61)

All data are expressed as n (%), mean ± standard deviation or median (1<sup>st</sup> quartile; 3<sup>rd</sup> quartile). eCC, estimated creatinine clearance; CG, Cockcroft-Gault; eGFR, estimated glomerular filtration rate; CKD-EPI, chronic Kidney Disease Epidemiology Collaboration NT-proBNP, N-terminal pro-brain natriuretic peptide.

## Supplementary appendix

**Table S2. Changes in cardiac, renal and adrenal magnetic resonance parameters between baseline, four months and 12 months after living kidney donation**

Variable	n	fu4 - baseline	n	fu12 - fu4	n	fu12 - baseline
LVM, g	23	1.6±1.0	23	1.5±1.1	23	3.1±1.4
LVM index, g/m <sup>2</sup>	23	1.2±1.3	23	0.2±1.2	23	1.4±1.1
LVM+ Pap, g	23	1.9±1.5	23	2.1±1.4	23	4.1±1.8
(LVM+Pap) index, g/m <sup>2</sup>	23	1.4±1.4	23	0.6±1.3	23	1.9±1.1
LVM/EDV, g/ml	23	0.01±0.07	23	0.05±0.08	23	0.06±0.09
SWT, mm	23	0.1±0.8	23	0.3±0.8	23	0.4±1.1
PWT, mm	23	0.0±1.3	23	0.6±1.6	23	0.6±1.4
Kidney volume, ml	23	31.4±13.7	22	3.1±12.0	22	34.5±11.6
Adrenal gland total, ml	22	0.51±1.16	23	0.50±1.65	22	0.83±1.66
Adrenal gland (left), ml	22	0.15±0.61	23	0.20±0.92	22	0.28±0.88
Adrenal gland (right), ml	22	0.36±0.84	23	0.30±0.89	22	0.55±0.96

All data are expressed as n (%), mean ± standard deviation or median (1<sup>st</sup> quartile; 3<sup>rd</sup> quartile).

LVM, left ventricular mass; Pap, papillary muscle mass; EDV, end-diastolic volume; SWT, side wall thickness; PWT, posterior wall thickness.

## ***Supplementary appendix***

**Table S3. Sub-analysis, intra-control group**

**Change of LVM between four months and one day prior to living kidney donation**

<b>Variable</b>	<b>4 months prior to LKD</b>	<b>1 day prior to LKD</b>	<b>difference</b>	<b>p-value</b>
LVM, g	117.0±25.0	116.8±25.3	-0.20±0.35	0.16
LVM + Pap, g	123.1±25.6	123.1±25.9	-0.01±0.72	0.96
LVM/EDV, g/ml	0.93±0.16	0.94±0.24	0.01±0.10	0.74

All data are expressed as n (%), mean ± standard deviation.

LKD, living kidney donation; LVM, left ventricular mass; Pap, papillary muscle mass;

EDV, end-diastolic volume.